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Statement on Safety Issues Related to Acetaminophen Before the Nonprescription Drugs Advisory Committee September 19, 2002

In 1977, the Food and Drug Administration's (FDA's) Advisory Review Panel recommended the following warnings for acetaminophen-containing products: "Do not exceed recommended dosage because severe liver damage may occur" and "Do not exceed recommended dosage or take for more than 10 days, because severe liver damage may occur." The FDA chose to ignore this wise advice.

A quarter of a century later we are facing an epidemic of fatal acetaminophen-associated poisonings: a near doubling from 76 in 1995 to 141 in 1999, according to data collected by the American Association of Poison Control Centers through its Toxic Exposure Surveillance System (TESS). TESS data also show 108,102 calls to Poison Control Centers in 1999, while data from the National Hospital Ambulatory Care Survey (NHAMCS) show an average of 56,680 Emergency Department Visits per year. The National Hospital Discharge Survey (NHDS) indicates that there are an average of 26,256 hospitalizations per year related to acetaminophen overdoses. Although the TESS data best indicate the time trend for acetaminophen-related mortality, the best estimate of the average number of deaths per year related to acetaminophen is 458, according to death certificate data. Acetaminophen is the leading cause of toxic drug ingestions in the U.S. By any measure, this is a major national health problem.

The FDA has estimated that between at least 57% and 74% of ingestions are intentional, yet the issue before this Committee is described as "Unintentional Acetaminophen Hepatotoxicity," an illogical restriction of the debate and seemingly a capitulation to the notion that nothing can be done for those making suicide attempts. This ignores the facts that many suicide attempts are impulsive "cries for help" (but may nonetheless be fatal), most are not fatal (but may leave significant residual disability), and fatality rates are related to doses consumed.

In fact, many countries have sought to address the problem of suicides or "intentional overdoses." A recent experiment of this kind in the United Kingdom, implemented in September 1998, restricted the number of acetaminophen tablets per pack to 16 in supermarkets and 32 in pharmacies. (Much of this was accomplished through the use of blister packs.) Although one can buy several packs, prescriptions are required to obtain more than 100 tablets. Early evaluations of the program show decreases in total and severe acetaminophen overdoses as well as decreases in acetaminophen-overdose liver transplants and deaths (Prince, et al. Lancet 2000;355:2047-8; Turvill, et al. Lancet 2000;355:2048-9; Robinson, et al. BMJ 2000;321:926-7; Hawton, et al. BMJ 2001;322:1203-7), although the results are not completely consistent between studies. Information on this critical experiment is not mentioned in the briefing material

posted on the FDA's website.

The following is a six-point plan to address the acetaminophen overdose problem in all its manifestations. While some primarily address intentional overdoses, many of these will also affect unintentional overdoses.

1. Consumer access to risk information

The currently required acetaminophen label is woefully inadequate, excluding even the liver-toxicity warning recommended a quarter of a century ago by the FDA's own advisers. In addition to including a general warning about liver toxicity, the label should mention the early symptoms of liver toxicity and instruct patients to discontinue the drug and seek medical attention should such symptoms appear. It should also warn against the simultaneous use of multiple acetaminophen-containing products. As many of these elements as possible should appear, in sufficiently large typeface, on the container itself, as has successfully been done with children's aspirin in the successful attempt to prevent Reye's Syndrome. If the box warning becomes unwieldy, consideration should be given to a system of rotating warnings, as has become standard on tobacco packs. A patient information leaflet in each package should also be mandated.

Other modes of communication should also be used to warn consumers. Advertising for acetaminophen-containing over-the-counter products (regulated by the Federal Trade Commission, not the FDA) should also require the warnings mentioned above. The FDA should also write articles in medical and lay journals to increase health professional and consumer awareness of the problem. Public Service Announcements are also an important part of such a strategy.

2. Reduce maximum daily doses

Among unintentional adult acetaminophen-related liver toxicity cases reported to the FDA or published in the medical literature (a total of 282 between January 1, 1998 and July 25, 2001), the median daily dose was 5 g/day (range: 0.65-30 g/day), not much above the FDA-recommended maximum of 4 g/day. Among those with a history of alcohol use, the median dose was 4.6 g/day, compared with 5.8 g/day among those without such a history. This argues strongly for a reduction in the maximum daily dose for alcohol users. Patients with liver toxicity and underlying liver disease also had consumed low daily doses of acetaminophen (median: 4 g/day) as did those taking potentially liver-toxic medications in addition to acetaminophen (median: 3.9 g/day); this argues for similar maximum daily dose restrictions in these populations. The margin of safety is even small for patients without these underlying conditions. Restrictions on daily doses should be considered for them too.

3. Reduce per-tablet doses

Because there is a strong relationship between the amount of drug consumed and the incidence of serious overdose and death, and because there is a practical limit on how many pills a suicidal patient can take, it is logical that a reduction in the strength of individual dosage forms to 325 mg per tablet would yield benefits. Such a restriction is likely to also benefit pediatric patients who ingest acetaminophen-containing products as well as those unknowingly taking multiple acetaminophen-containing products. There is precedent for such a restriction. Over-the-counter ibuprofen contains only 200 mg of the drug, compared with up to 800 mg in the prescription versions.

4. Standardize liquid formulations

Cases of liver toxicity reported to the FDA or reported in the medical literature between January 1, 1998 and July 25, 2001 included 25 pediatric cases. In at least four of these, teaspoonfuls of medication were administered, instead of dropperfuls. While acetaminophen suspension contains 32 mg/ml, the drops contain 100 mg/ml, ample opportunity for unintentional overdose. All liquid forms of the drug should be required to have the same concentration.

5. Remove irrational acetaminophen-containing combinations from the market

Forty-nine percent of over-the-counter acetaminophen sales is in the form of combination products. Most, if not all, of these combinations are irrational. Patients (and their parents) should be encouraged to use only the medication they need, not lapse into this shotgun approach to drug therapy. The use of combination products with elaborate (often misleading) brand names discourages patients from learning the generic names of active ingredients, potentially leading to overdoses when taken with other acetaminophen-containing drugs. Approximately 25% of patients with liver toxicity collected by the FDA had taken more than one acetaminophen-containing product.

6. More research

It has been suggested that all acetaminophen-containing products be combined with N-acetylcysteine, the drug used to treat acetaminophen overdose. While we are aware of no studies documenting the effectiveness of this approach, it does merit further study. The impact of any interventions to reduce acetaminophen-related liver toxicity adopted by the FDA should also be measured so that new measures can be added if appropriate.

None of these approaches will be enough on its own to eliminate acetaminophen overdoses. Only a multidimensional approach is likely to significantly reduce the enormous burden of suffering and the expenditure of scarce health care resources currently represented by this in-large-part preventable problem.